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Soldier Health • World Health



Rickettsial Diseases and Lyme (AFRICOM focus)

LTC Paige Waterman, MD

Objectives

- Familiarization with:
 - Classification
 - Clinical presentations
 - Disease specific features (risk factors, treatment)
- Clinical case exercises

Common rickettsial infections

	TICK-BORNE	FLEA-BORNE	LOUSE-BORNE	MITE-BORNE
RICKETTSIAE				
SPOTTED fever group	<i>R. rickettsii</i> <i>R. conorii</i> <i>R. Japonica</i> <i>R. africae</i> <i>R. parkeri</i>	<i>R. felis</i>		<i>R. akari</i>
TYPHUS group		<i>R. typhi</i>	<i>R. prowazekii</i>	
Scrub typhus (<i>Orientia</i>)				<i>O. tsutsugamushi</i>
Anaplasma	<i>A. phagocytophilum</i>			
Ehrlichia	<i>E. chafeensis</i> <i>E. ewingii</i> <i>E. canis</i>			
Q Fever	<i>Coxiella burnetii</i> *			
(Lyme)	<i>B. burgdorferi</i>			

Common things being common

Destination	No. travelers						
	SFG rickettsiosis	TG rickettsiosis	Indeterminate SFG/TG rickettsiosis	Scrub typhus	Anaplasmosis	Acute Q fever	Bartonellosis
Western Europe	7	1			1	2	1
Eastern Europe			1				
North Africa	3						
Sub-Saharan Africa	197	1				5	1
Middle East	1					2	1
Northeast Asia	2	1				1	
South central Asia	5	1	1	5			
Southeast Asia	3	6	2	9			1
Australia/New Zealand	1			1			
Oceania	1						
North America	1						
Central America	3						
Caribbean	1						3
South America							
Unknown	6			1		1	
Total	231	10	4	16	1	11	7

*SFG, spotted fever group; TG, typhus group.

Spotted fever group

Tick

Flea

Mite

R. rickettsii

R. felis

R. akari

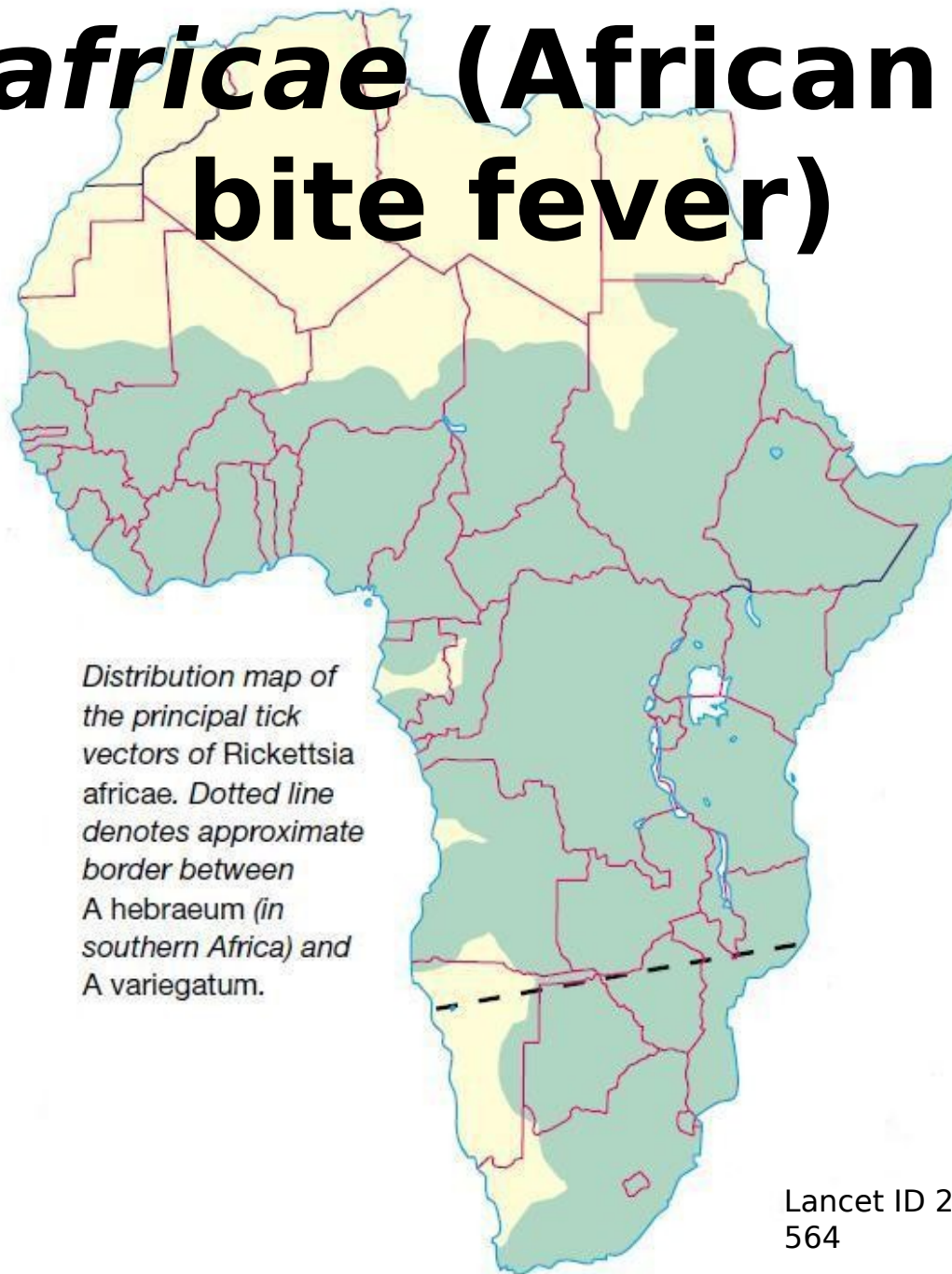
R. conorii

R. Japonica

R. africae

R. parkeri

***R. africae* (African tick bite fever)**



Distribution map of the principal tick vectors of Rickettsia africae. Dotted line denotes approximate border between A hebraeum (in southern Africa) and A variegatum.

***R. africae* (African tick bite fever)**

- Incubation 5-7 days
- Acute, febrile, and influenza-like
- Frequently with severe headache
- Prominent neck muscle myalgia/s
- Inoculation eschar/s (black crusts surrounded by a red halo)
- +/- vesicular rash/aphthous ulcers
- Regional lymphadenitis
- ~50% of patients have multiple eschars

***R. africae* (African tick bite fever)**



***R. africae* (African tick bite fever)**

- Ecology of exposure: soldiers, safaris, camping, exposure in cattle farming areas
- Diagnosis: tough (clinical)
- Treatment: doxycycline 100mg BID 7d (48hrs post defervescence)
- Prevention: PPE

***R. conorii* (Mediterranean spotted fever AKA Boutonneuse fever)**

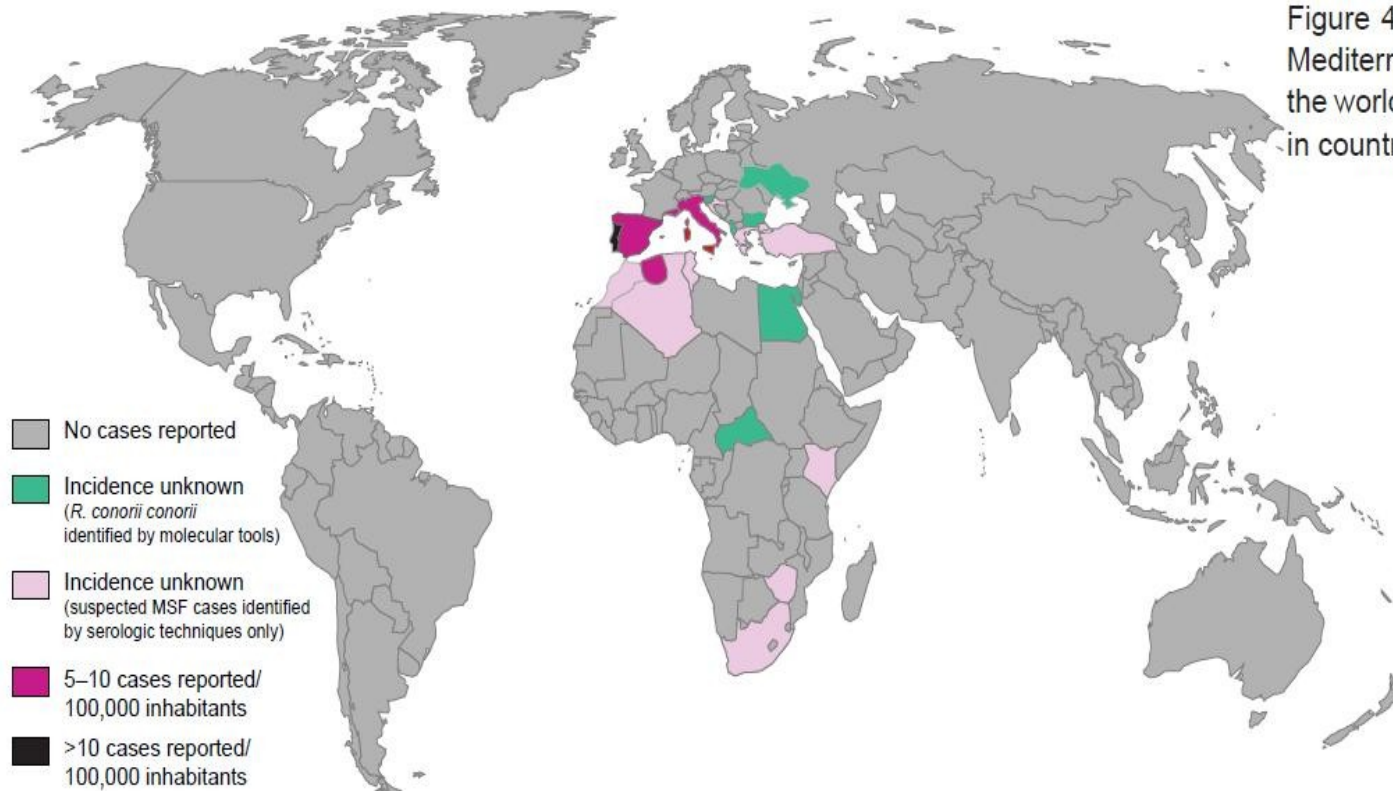


Figure 4. Distribution of the cases of Mediterranean spotted fever (MSF) in the world and incidence of the disease in countries where MSF is endemic.

R. conorii (Mediterranean spotted fever AKA Boutonneuse fever)

		Symptoms present, % patients			Fatal forms? (% patients)			Fatal forms? (% patients)
		Fever	Inoculation eschar	Rash				
<i>Rickettsia</i>	Vector	91–100	20–87	93–100	Yes (0–18.1)			
<i>R. conorii conorii</i> , isolates Malish, Moroccan Kenyan	<i>Rhipicephalus</i> sp. <i>Haemaphysalis</i> lea					7	93–100	Yes (0–18.1)
<i>R. conorii israelensis</i>	<i>Rh. sara</i>	100	0–40	98–100	Yes (0–3.5)		98–100	Yes (0–3.5)
<i>R. conorii caspia</i>	<i>Rh. sanguineus</i>	100	23	94	No		94	No
<i>R. conorii indica</i>	<i>Rh. sanguineus</i> <i>Boophilus microplus</i> <i>leish</i>	100	Rare	100 (frequently purpuric)	No		100 (frequently purpuric)	No

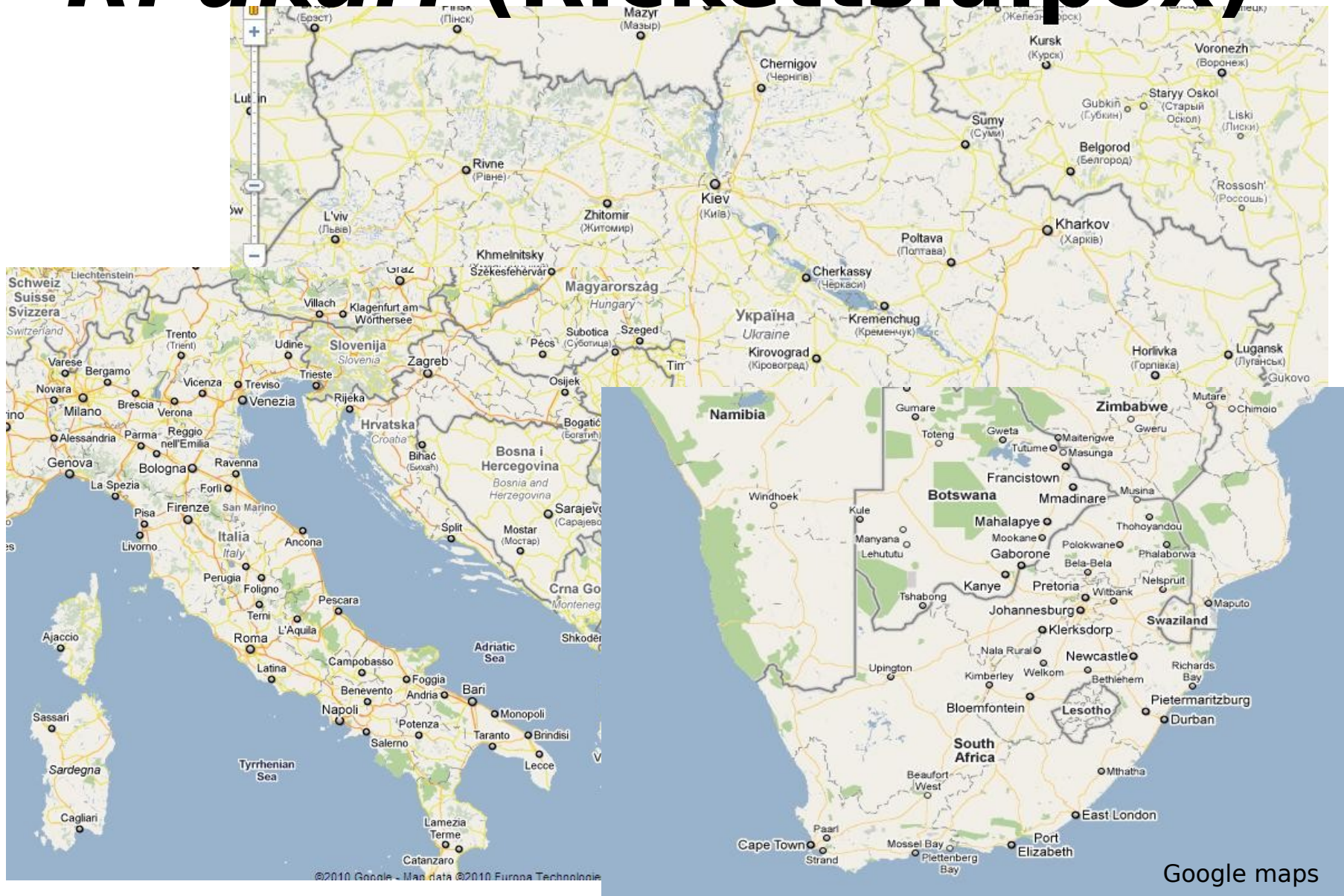
Unlike African tick bite fever, eschars RARELY multiple in MSF

Tâche
noire

***R. conorii* (Mediterranean spotted fever AKA Boutonneuse fever)**

- Incubation 5-7 days
- Ecology of exposure: peridomestic; buildings where dogs kept
- Diagnosis tough (clinical) +/- biopsy (eschar); serology (IFA), PCR, culture
- Treatment: doxy 100mg BID 5-10 days
- Prevention: PPE

R. akari (Rickettsialpox)



***R. akari* (Rickettsialpox)**

- Incubation 9-14 days
- Papulovesicular eruption (rash) after 2-3 days
 - Trunk, extremities, oral mucosa
- Eschar develops (at site of bite/rash)
- Fever (3-7 days after skin lesion)
- Generalized lymphadenopathy
- Self-limited (14-21 days)

***R. akari* (Rickettsialpox)**



J Am Acad Dermatol
2004;51:S137-42
healthfiles.net/disease/category/r

***R. akari* (Rickettsialpox)**

- Ecology of exposure: mouse infested urban areas
- Diagnosis tough (clinical): low WBC, mild proteinuria, thrombocytopenia
- Treatment: doxycycline 100mg BID until clinically improved 48hrs (~ 5-7 days)
- Prevention: PPE

“Pox” DDX

Feature	Rickettsialpox	Chickenpox ²⁴	Smallpox (variola major) ²⁵
Eschar	Yes	No	No
Incubation period	9-14 days	14 days (range 10-23)	12 days (range 10-14)
Prodrome	Usually mild, may be severe. Fever, malaise, and headache.	Absent or mild and brief (less than one day)	Usually severe with high fever, headache, backache. Vomiting and severe abdominal pain may be present. Lasts 2 to 4 days.
Timing and evolution of lesions	Lesion develops at the site of the bite within 24 to 48 hrs and evolves into eschar. Rash begins 2 to 3 days after prodrome. Papules may eventuate in papulovesicles.	Lesions occur in “crops” over 2 to 4 days. Different stages characteristic: macules, papules, vesicles, pustules, crusts	Emerge over 1-2 days and then progress at same rate. The lesions progress over several days from macules (day 1), to papules (day 2), to vesicles (days 3-5), to pustules (days 7-14), to scabs (day 14-20).
Pruritus/pain	Exanthem usually asymptomatic: occasional pruritus.	Commonly pruritic	Pruritic during healing, otherwise may be painful.
Distribution	Anywhere. Palms, soles not usually involved.	Starts on trunk and face and spreads centrifugally. Palms, soles may be involved	Begins on the oral mucosa, face, and extremities and spreads centripetally. Palms, soles commonly involved.
Enanthem	Minority of cases.	Common, especially palate.	Starts in mouth
Scarring	Eschar leaves depressed scar, papulovesicles do not.	If bacterial superinfection occurs	Yes

Typhus group

Flea

Louse

Chigger mite

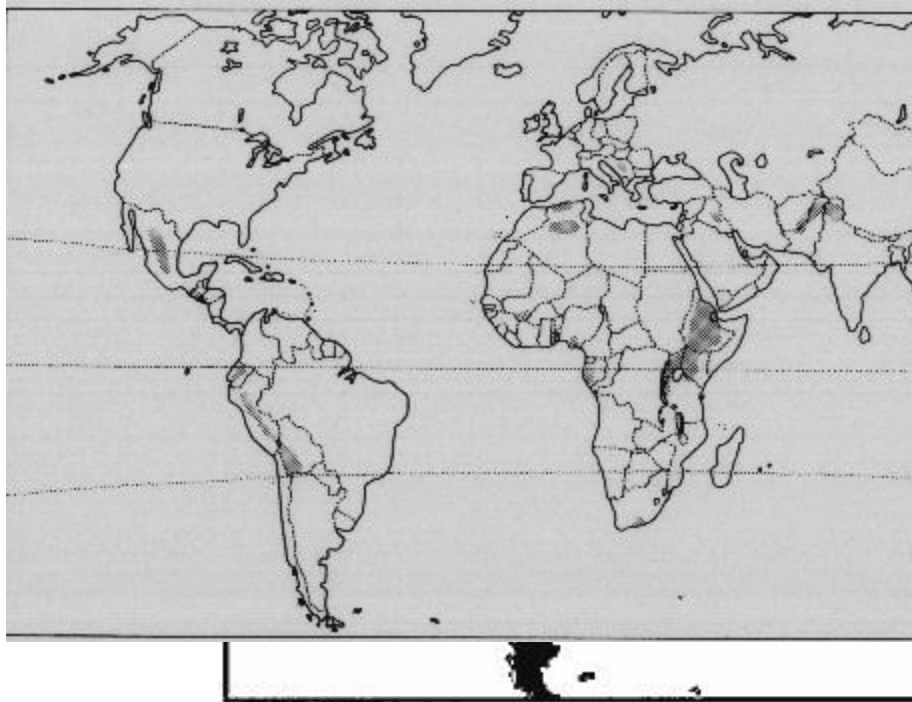
R. typhi

R. prowazekii

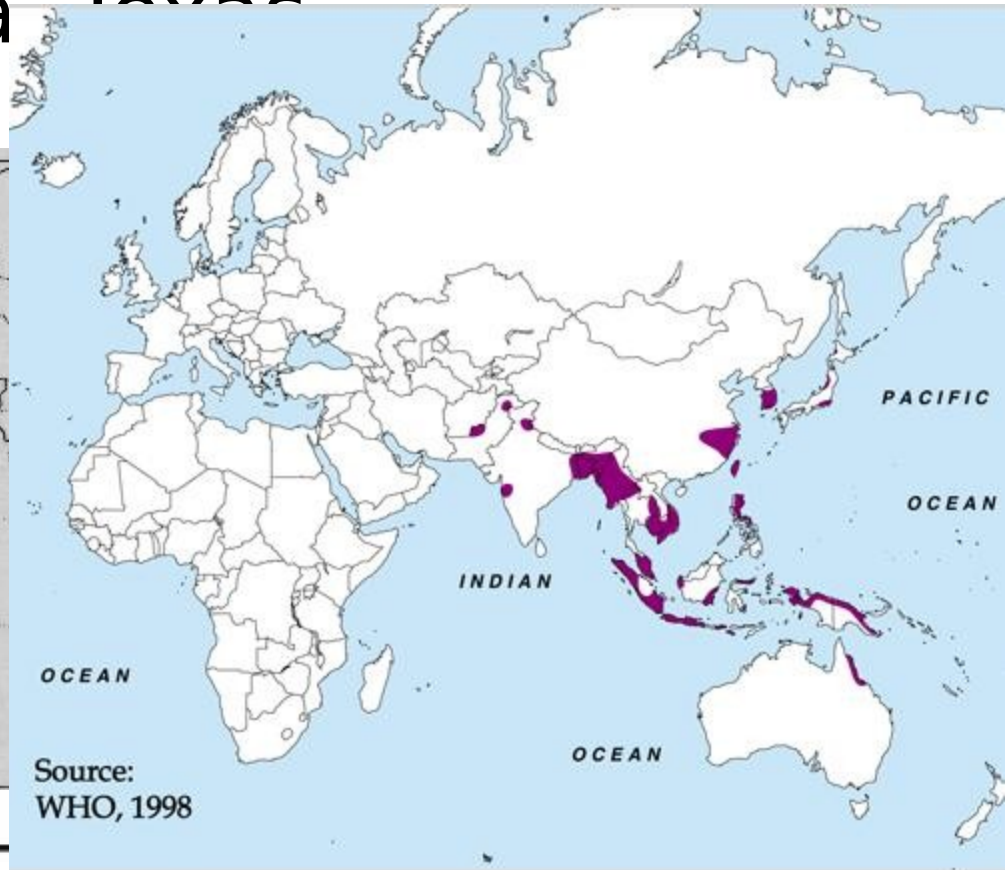
O. tsutsugamushi

***R. typhi* (murine/endemic typhus)**

- Asia, Africa, S. Europe (coastal)
- Hawaii, California, Texas
- Rats



WHO, 1998



LID. 1998,4(4):677-680

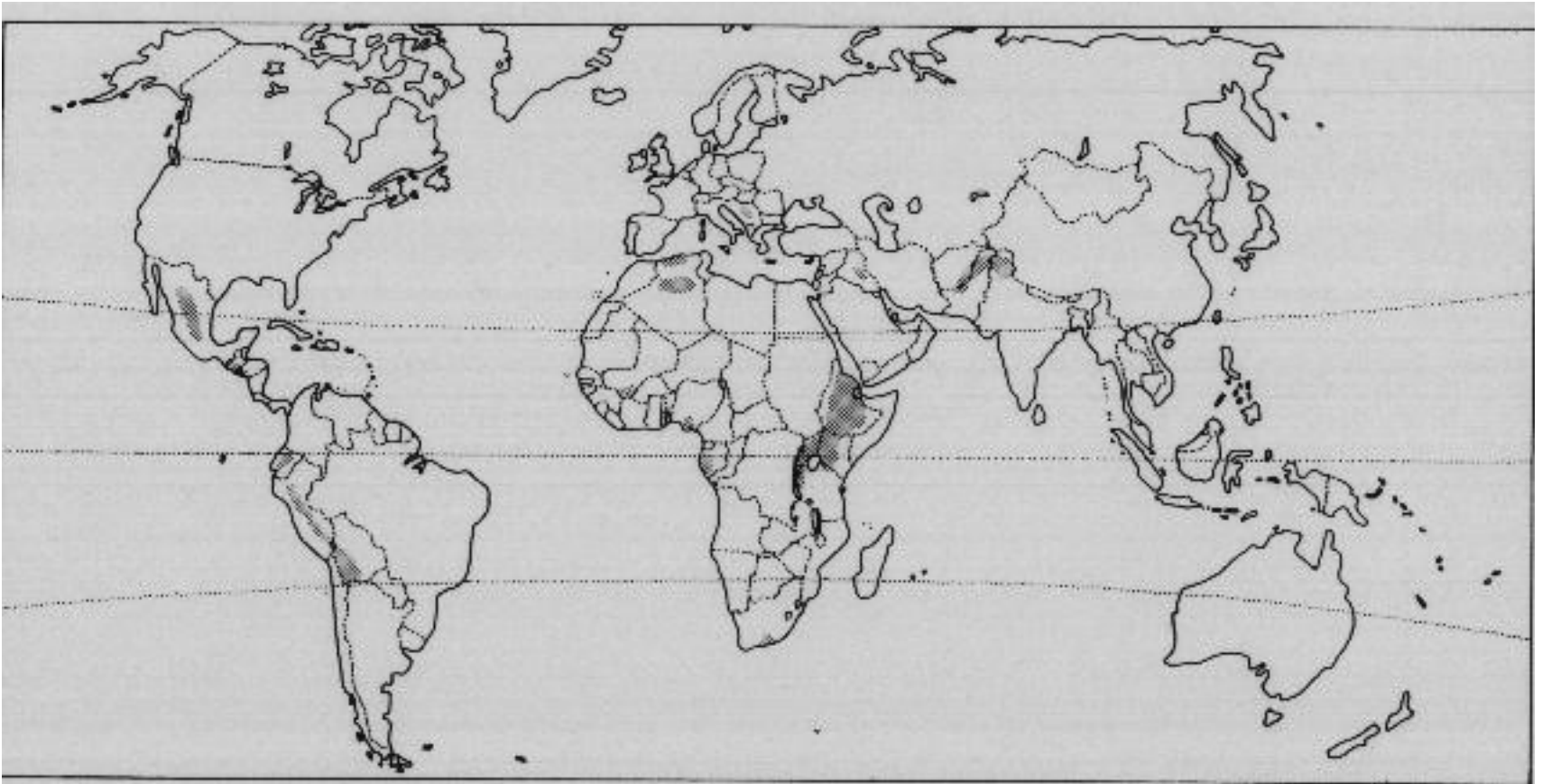
***R. typhi* (murine/endemic typhus)**

- Flea bites (infected feces contaminates skin) or aerosolization
- Incubation 6-14 days
- Fever, headache, rash 50%
- Leukocytosis or mild leukopenia
- Anemia
- +/- hyponatremia, hepatic/renal abnormalities

***R. typhi* (murine/endemic typhus)**

- Ecology of exposure: rat fleas; coastal areas
- Diagnosis (clinical): serology (immunofluorescence) esp. with recurrent dz
- Treatment: doxycycline 100mg BID for 48-72hrs after fever resolved
- Prevention: PPE

***R. prowazekii* (louse-borne/epidemic)**



WHO, 1998

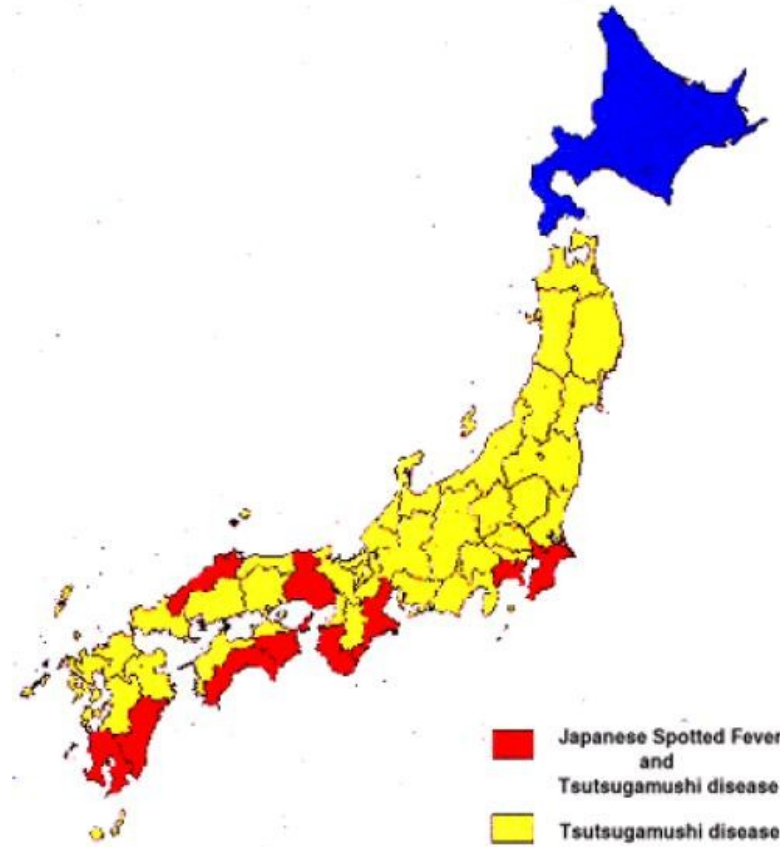
***R. prowazekii* (louse-borne/epidemic)**

- Incubation 6-14 days
- Fever, headache (abrupt), myalgias
- Rash (mac-pap/petechial) on days 4-7 axilla/trunk and spreads peripherally (UNLIKE RMSpF)
- CNS symptoms (incl. coma)
- Can see shock (multifocal/multi-organ vasculitis)

***R. prowazekii* (louse-borne/epidemic)**

- Only typhus group with humans as usual host
- Ecology of exposure: crowded, war/disasters, lacking water; body lice
- Diagnosis: serology (IFA), biopsy, PCR
- Treatment: doxycycline (as endemic)
- Prevention: PPE

***O. tsutsugamushi* (Scrub typhus)**



***O. tsutsugamushi* (Scrub typhus)**

- Eschars (tâche noire) from painless papule
- Fever, chills, headache, conjunctival suffusion
 - All prior to centrifugal rash
- Cough & tachypnea (pulm. involvement)
- Regional lymphadenopathy
- +/- diminished hearing

***O. tsutsugamushi* (Scrub typhus)**

- Ecology of exposure: forest re-growth (walking); plantations; river banks; building sites/clearings
- Diagnosis (clinical); devel. rapid diagnostics
- Treatment: doxycycline (can be RESISTANT)
- Prevention: PPE

Ehrlichia and Anaplasma

E. chafeensis

E. ewingii

E. canis

Ehrlichiosis

HME	HGA	<i>E. ewingii</i>
1987	1994	1999
<i>E. chaffeensis</i>	<i>A. Phagocytophilum</i>	<i>E. ewingii</i>
Monocyte macrophage	Granulocyte	Granulocyte
>1600	>2100	~20
SC, SE, mid-Atl	NE, MW, Pac coast	SC (S. central)

Military importance (Ehrlichiosis)

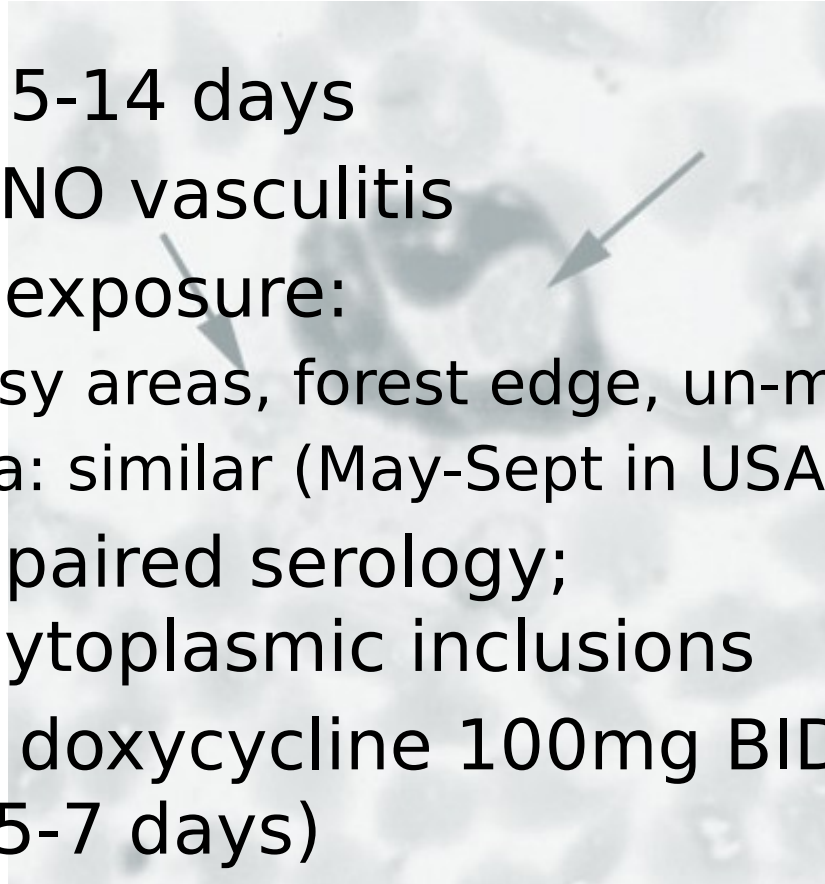
Group, disease	Causative agent	Mode	Geographic
Canine	<i>E. canis</i>	Tick bite	SE Asia, SW US, Venezuela
HME	<i>E. chaffeensis</i>	Tick bite	Americas, Europe, Thailand
HGA	<i>A. phagocytophilum</i>	Tick bite	USA, Europe, Asia
Sennetsu fever	<i>Neorickettsia sennetsu</i>	unknown	Japan, Malaysia

Ehrlichia - disease symptoms

Symptom, sign, or finding	Patients, % (no. evaluated)	
	HME	HGA
Symptom or sign		
Fever	97 (633)	93 (521)
Myalgia	57 (250)	77 (516)
Headache	80 (240)	76 (385)
Malaise	82 (234)	94 (288)
Nausea	64 (143)	38 (258)
Vomiting	33 (192)	26 (90)
Diarrhea	23 (197)	16 (95)
Cough	26 (155)	19 (260)
Arthralgias	41 (211)	46 (504)
Rash	31 (286)	6 (357)
Stiff neck	3 (240)	21 (24)
Confusion	19 (279)	17 (211)
Laboratory finding		
Leukopenia	62 (276)	49 (336)
Thrombocytopenia	71 (247)	71 (336)
Elevated serum AST or ALT level	83 (276)	71 (177)

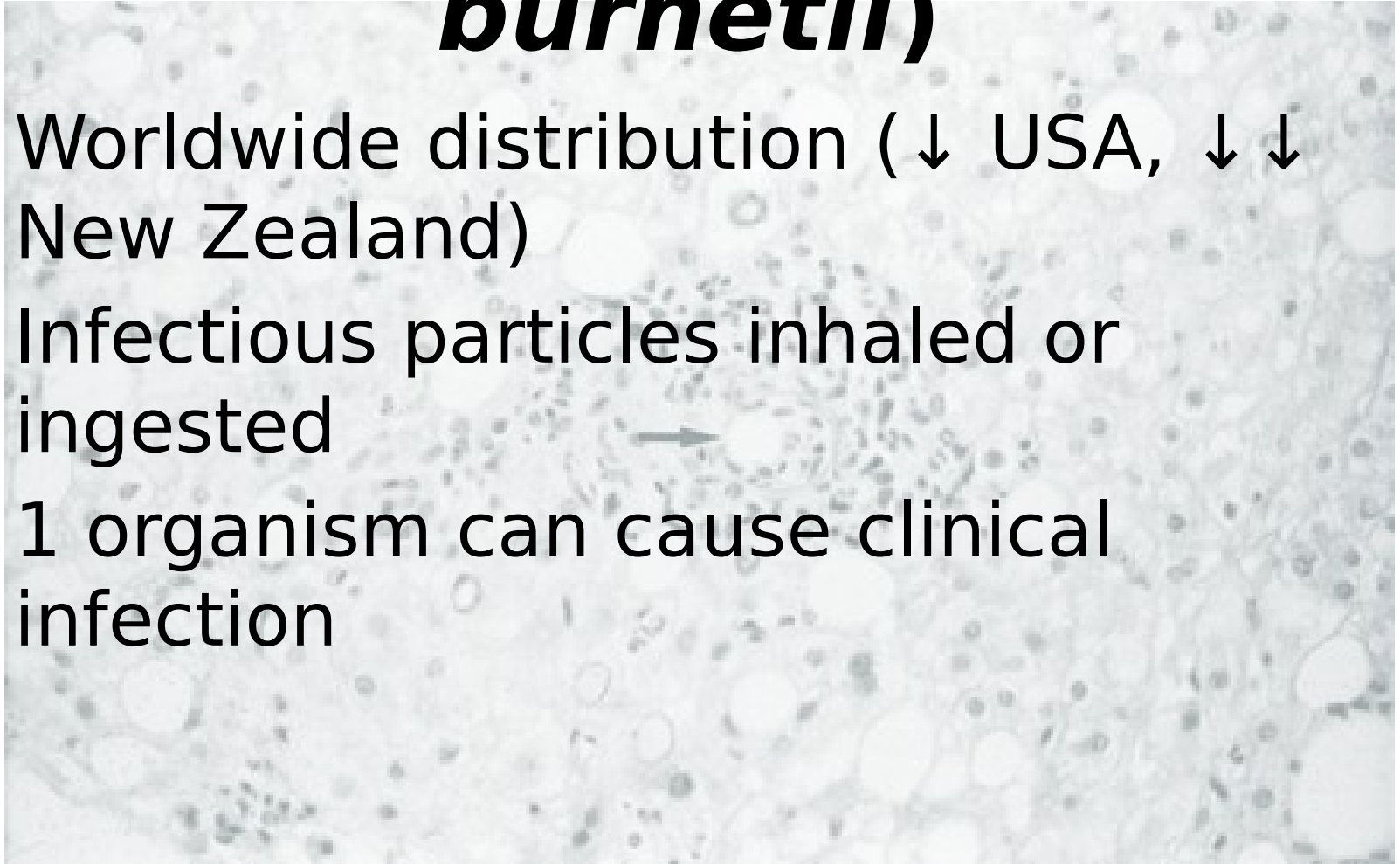
Ehrlichiosis

- Incubation 5-14 days
- Rash rare; NO vasculitis
- Ecology of exposure:
 - HME: grassy areas, forest edge, un-mowed areas
 - Anaplasma: similar (May-Sept in USA)
- Diagnosis: paired serology;
morulae=cytoplasmic inclusions
- Treatment: doxycycline 100mg BID ~ 3d after
afebrile (~5-7 days)
- Prevention: PPE



Q fever (*Coxiella burnetii*)

- Worldwide distribution (↓ USA, ↓ ↓ New Zealand)
- Infectious particles inhaled or ingested
- 1 organism can cause clinical infection





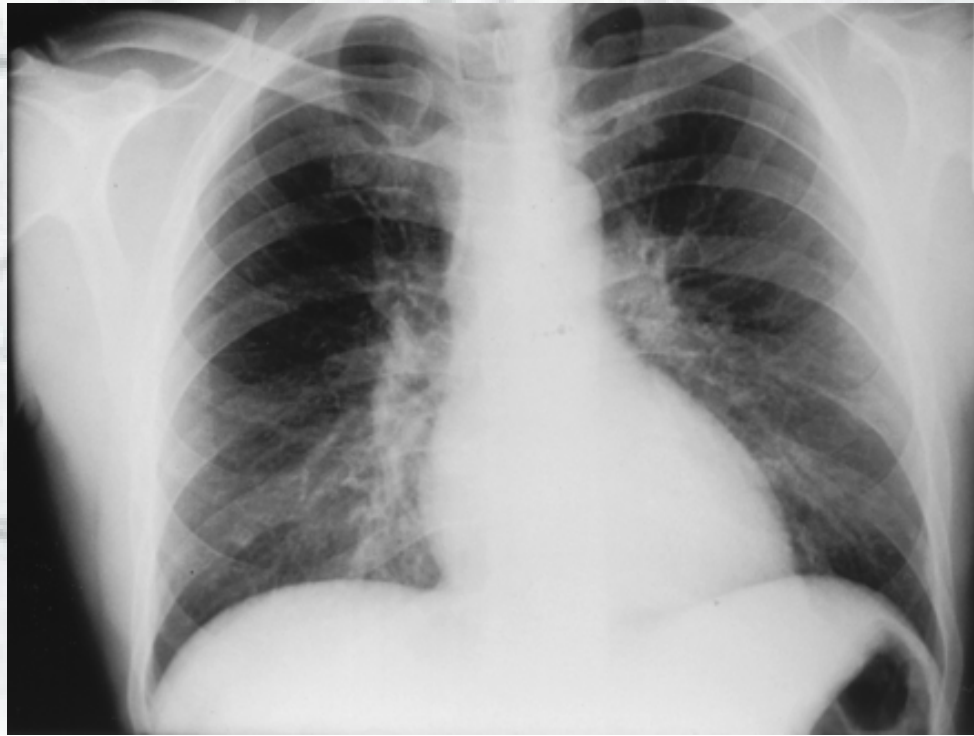
From Lancet 1984: 12 people were playing poker in the same room as a parturient cat. All 12 handled either the cat or litter and all 12 were diagnosed with acute Q fever (placentas carry 10^9 organisms).

Q fever (*Coxiella burnetii*)

- 3 clinical presentations (major)
 - Febrile illness
 - Pneumonia (with fever)
 - Hepatitis (with fever)
 - * 60% asymptomatic
- Endocarditis (may be chronic)

Q fever (*Coxiella burnetii*)

- Atypical pneumonia



Q fever (*Coxiella burnetii*)

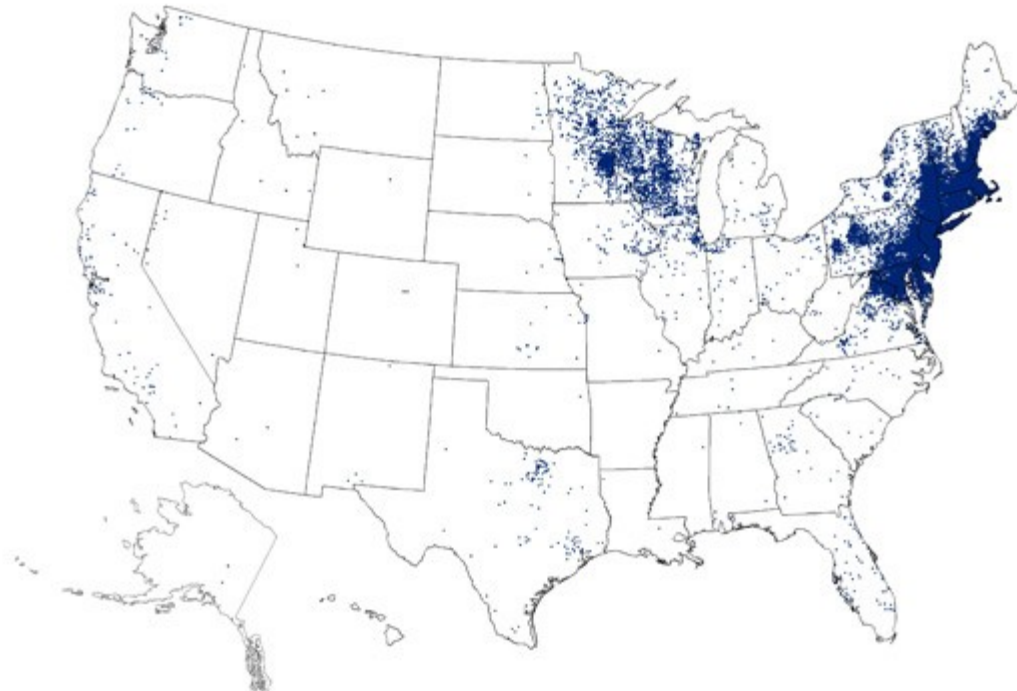
- Ecology of exposure: farmers, vets, abattoir and lab workers
- Diagnosis: paired serology (Ph II, Ph I)
- Treatment: 100mg Doxy BID 14-21 days
- PPE: educate (livestock, dairy)
disposal birth products (animals)
quarantine/restriction of infected animals
caution high risk folks (valve disease)



"And I want that guy tested for Q fever !"

Lyme disease (*B. burgdorferi*)

Reported Cases of Lyme Disease -- United States, 2008



1 dot placed randomly within county of residence for each confirmed case

Common presenting symptoms

- Rash ~ 70-80% of infected persons
 - Begins at the site of a tick bite after a delay of 3-30 days
 - Gradually expands over a period of several days, reaching up to 12 inches (30 cm) across
 - Center of the rash may clear as it enlarges (Bull's-eye). It may be warm but not usually painful. Some patients develop additional EM lesions in other areas of the body after several days.
- +/- fatigue, chills, fever, headache, and muscle and joint aches, and swollen lymph nodes
- In context of outdoor exposure

Lyme disease (*B. burgdorferi*)



Lyme disease (*B. burgdorferi*)

Treatment:

- Erythema migrans: doxycycline 100mg PO BID (10-14 days)
- Meningitis or radiculopathy: ceftriaxone x 14 days (range 10-28 days)
- Cranial nerve palsy: doxy x 14 days (range 14-21 days), some use parenteral regimen especially if abnl CSF seen
- Cardiac disease: oral or parenteral regimen 14 days (range 14-21 days)
- Arthritis (late lyme disease):oral regimen 28 days
- Recurrent arthritis after oral regimen: repeat oral 28 days course or parenteral regimen 14-28 days
- CNS or peripheral nervous system disease: parenteral regimen 14 days (range 14-28 days)
- Acrodermatitis chronica atrophicans(seen mostly in Europe): oral regimen 21 days (14-28 days)

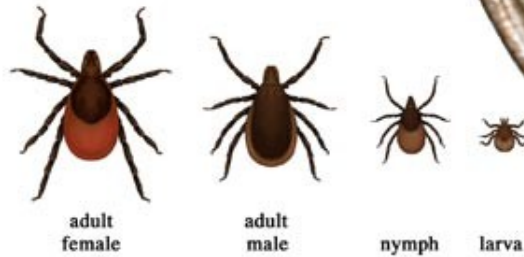
Prevention:

PPE (tick checks, permethrin, DEET, doxy 200mg x1 within 72hrs)

Size comparison



Blacklegged Tick (*Ixodes scapularis*)



Lyme
Ehrlichia
Anaplasma

Lone Star Tick (*Amblyomma americanum*)



Ehrlichia
Anaplasma
(white-tailed deer)

Dog Tick (*Dermacentor variabilis*)



Rocky Mt
Spotted
Fever

Matching

-
1. Rat-infested grain stores
2. Close living quarters, poverty
3. Sheep or cattle exposure
4. Transitional vegetation
5. Land navigation exercises
- A. Spotted fever (*R. rickettsia*)
- B. Q fever (*C. burnetii*)
- C. Scrub typhus (*O. tsutsugamushi*)
- D. Murine typhus (*R. typhi*)
- E. Louse-borne Typhus (*R. prowazekii*)

Case #1

- 35yo USMC medic in Iraq x 7 months
- En route CONUS – fever 104°F
- Now daily fever/chills + retro-orbital HA, lower back and bilateral calf pain
- ROS: sore throat, watery diarrhea x6 days
- Exposures: insect bites, slept in revamped Iraqi chicken factory, goats roaming, walked in brackish water, ate local Iraqi-prepared food

Case #1

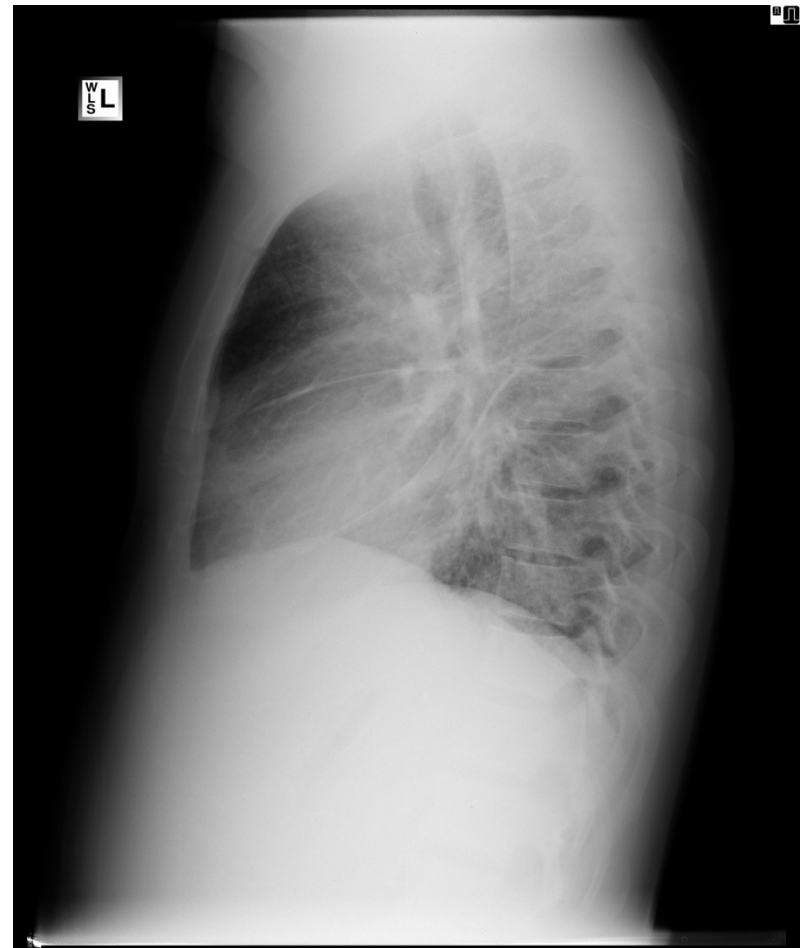
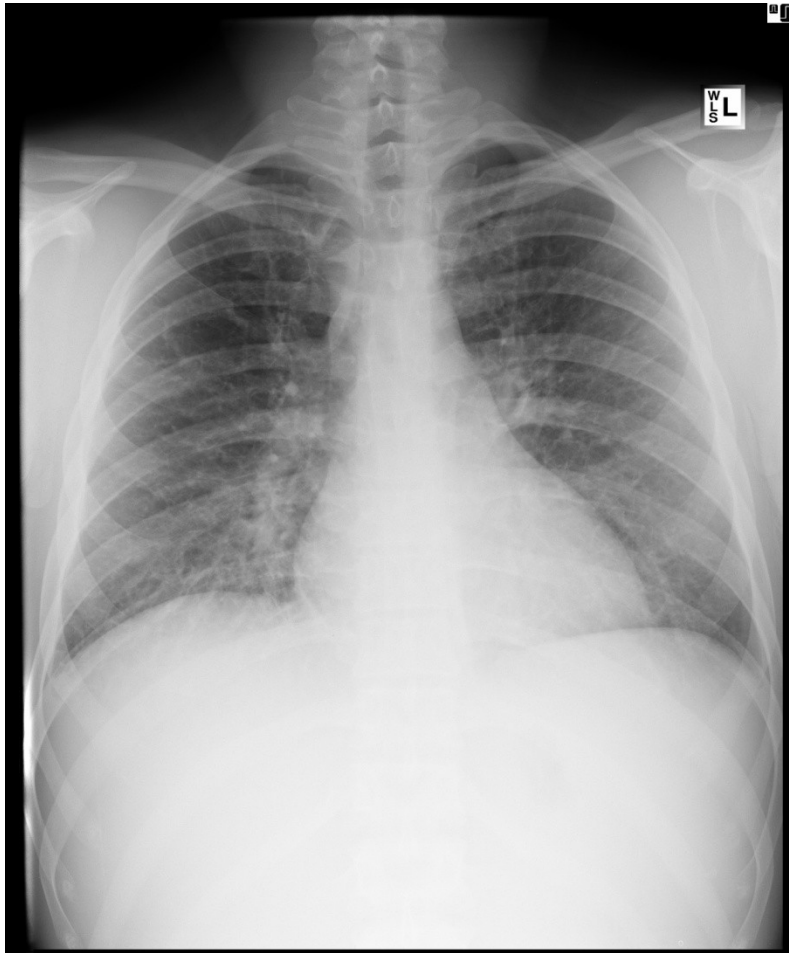
- PE:
 - T-103°F, HR-90, BP-110/60, O2sat-99% (RA)
 - Unremarkable
- CXR, abd CT both normal

Case #1 part B

- 23yo USMC – becomes ill 3 days after #1
- Similar fever, chills, sore throat, diarrhea
- ROS: blisters on feet (waded through sewage); only ate MREs, did not sleep in chicken factory (500yds away)
- PE: T-106°F, HR-104, BP-120/70, O2-98%
 - Mild jaundice o/w normal

Case #1B

CXR: bilat interstitial markings



Lab data

Patient 1

- **Na-130** (137-145)
- **K-3.0** (3.6-5.0)
- **Alkphos-310** (36-126)
- **AST-125** (17-49)
- **ALT-130** (7-56)
- **Tbili 1.8** (0.2-1.3)
- WBC 3.6 (4.0-11.0)
74N/E2
- Plt-120 (150-450)

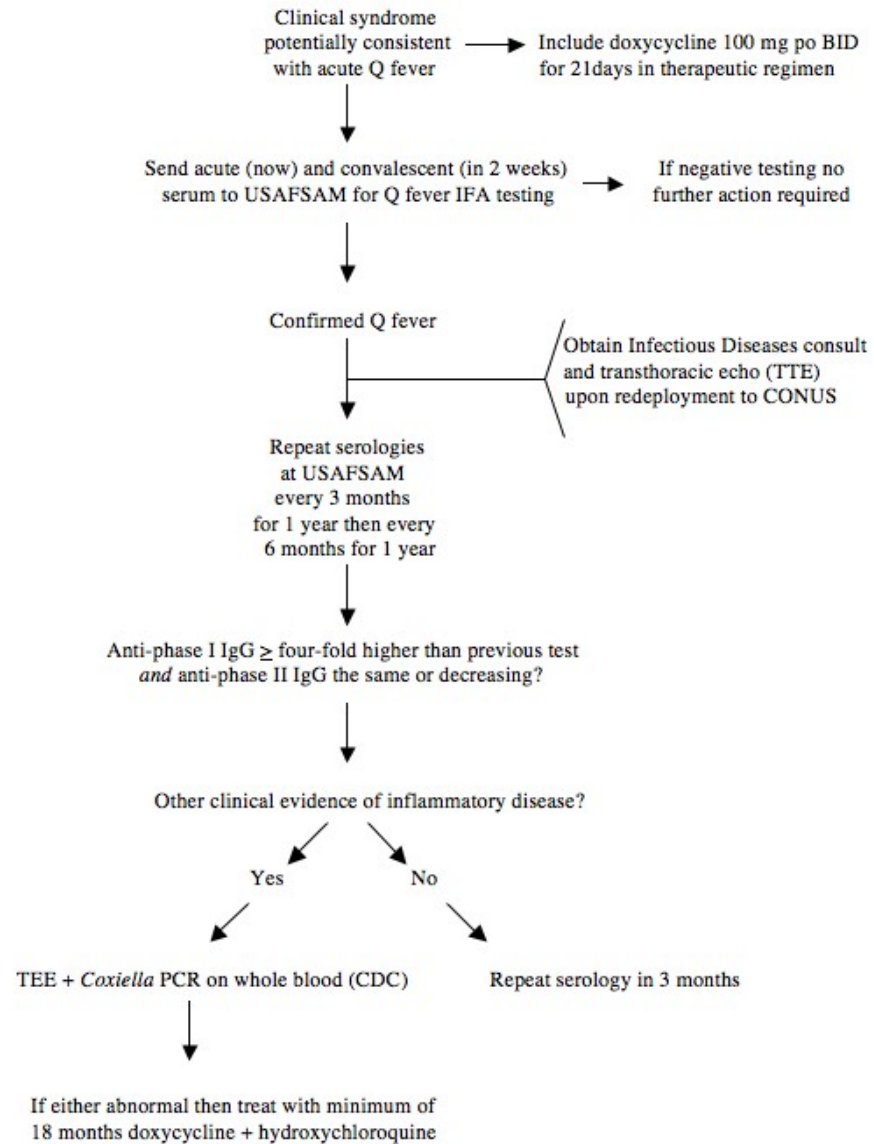
Patient 2

- **Na-130**
- **K-2.9**
- **Alkphos-137**
- **AST-173**
- **ALT-131**
- **Tbili-2.8**
- WBC-3.8
- **Plt-45**

Case #1

- Differential?
- Malaria smears (-)
- Blood, stool, urine cultures (and CSF #1) (-)
- Acute HIV, RPR (-)
- Viral, Dengue, Lepto, Hepatitis A/B/C (-)
- **Q fever**

Current Recommendations of the Tri-Service Infectious Diseases Q Fever Working Group



Case #2

- 44yo Indian subsistence farmer with fever x 7days
- Fever unremitting, initially abrupt onset
- Previously well
- One day severe frontal HA, N/V, photophobia, DOE and now tender swelling in left groin

TAMIL NADU



ROS

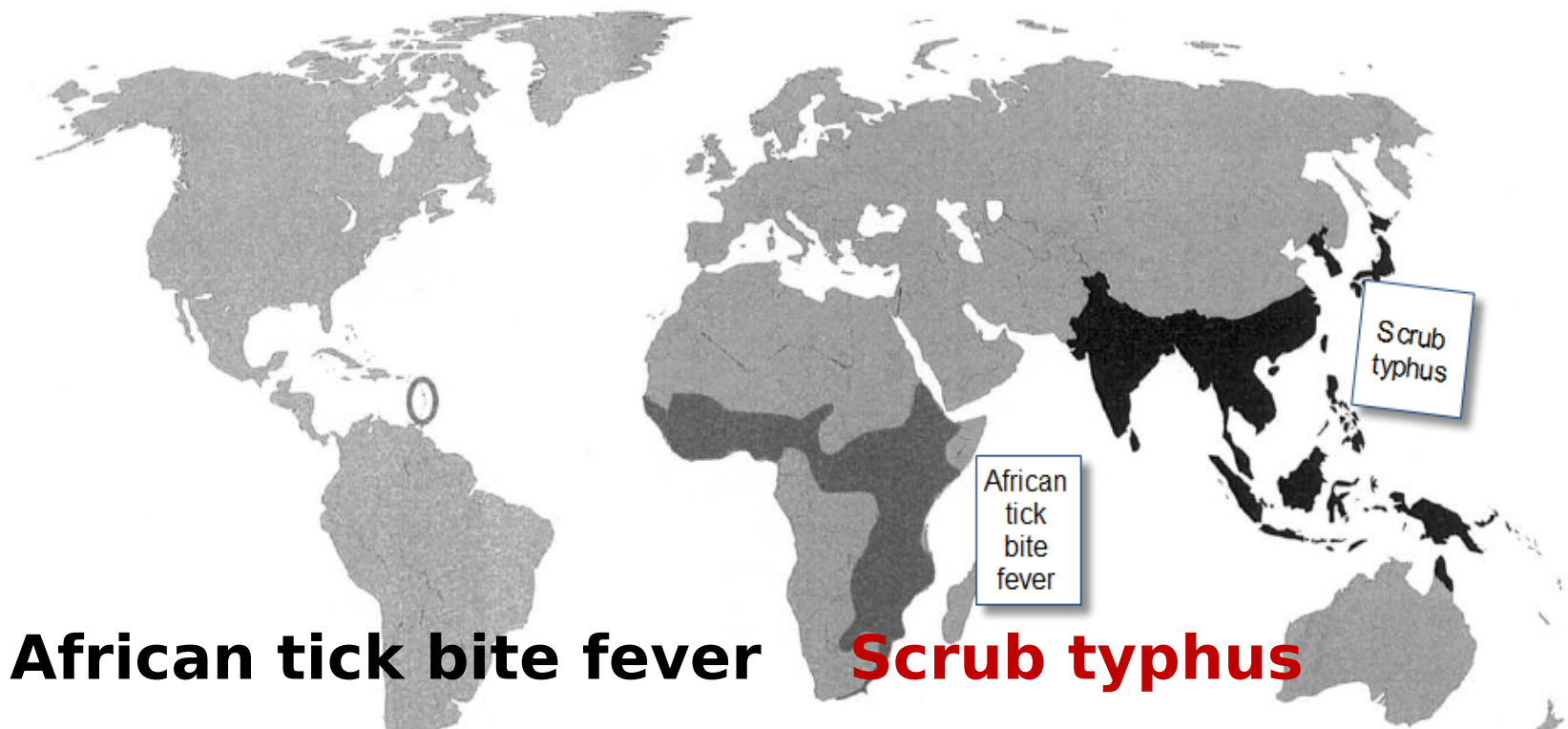
- No travel
- Chickens on farm
- Married, 2 children – all healthy
- Vegetarian; makes yogurt
- Water – well or river (wife gathers)
- No TOB, ETOH, drugs, meds, allergies
- Childhood vaccines (WHO) completed



Courtesy: N. Aronson, MD

More clinical information

- Following incubation (6-21 d), sx appear
- After initial sx (F, HA, chills, fever, ↺ hearing, conjunctivitis/suffusion, LAD), ulcer seen then centrifugal rash within 1 wk
- 2nd wk (if untreated):
 - Splenomegaly
 - Pneumonia
 - Myocarditis
 - Delirium
 - Death
- Diagnosis?



African tick bite fever

- *Amblyomma* tick
- ☂ tourists (~5%)
- HA, myalgias, eschar/s
- Vesicular rash, mouth blisters 30%
- Reactive arthritis (5%)
- Self-limited

Scrub typhus

- *Orientia tsutsugamushi*
- Loggers, rice farmers, military
- F, LAD (70%), eschar (50%)
- PNA, CNS, DIC, renal failure
- Indep. predictor mort: met. acidosis (in ast, who D_{elt})

CID 2004

Case #3

40yo male Thai subsistence farmer is brought to clinic with report of headache, chills, hearing loss, and cough. You note an eschar on his leg and elicit confusing responses to simple questions. What would be your drug of choice for treatment?

- A. Doxycycline
- B. Atovaquone
- C. Azithromycin
- D. Gentamicin

40yo male Thai subsistence farmer is brought to clinic with report of headache, chills, hearing loss, and cough. You note an eschar on his leg and elicit confusing responses to simple questions. What would be your drug of choice for treatment?

- A. Doxycycline
- B. Atovaquone
- C. **Azithromycin**
- D. Gentamicin

Case #4

A 44-year-old male traveler returning from Tanzania presents 7 days after return with fever and respiratory symptoms. Among rickettsial diseases to be considered, which of the following is most likely to be the cause of his illness?

- A. Ehrlichiosis
- B. Spotted fever group rickettsiosis
- C. Bartonellosis
- D. Typhus group rickettsiosis

A 44-year-old male traveler returning from Tanzania presents 7 days after return with fever and respiratory symptoms. Among rickettsial diseases to be considered, which of the following is most likely to be the cause of his illness?

A. Ehrlichiosis

B. Spotted fever group rickettsiosis

C. Bartonellosis

D. Typhus group rickettsiosis

#5

Which of the following is the most commonly used treatment for rickettsial disease among returning international travelers?

- A. Tetracycline
- B. Minocycline
- C. Septra
- D. Doxycycline

Which of the following is the most commonly used treatment for rickettsial disease among returning international travelers?

A. Tetracycline

B. Minocycline

C. Septra

D. Doxycycline

#6

During war with many displaced people, which organism would you be most concerned about because of its high mortality rates, complications, and epidemic potential?

- A. *Orientia tsutsugamushi*
- B. *Rickettsia rickettsia*
- C. *Rickettsia prowazekii*
- D. *Rickettsia typhi*

#6

During war with many displaced people, which organism would you be most concerned about because of its high mortality rates, complications, and epidemic potential?

- A. *Orientia tsutsugamushi*
- B. *Rickettsia rickettsia*
- C. *Rickettsia prowazekii***
- D. *Rickettsia typhi*

References

- <http://chppm-www.apgea.army.mil/DEP/default.aspx>
- <http://cdc.gov/>
- <http://afpmb.com/>



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• QUESTIONS?



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Ehrlichia disease

HME

- Fever (>95%), HA (60-75%), myalgias (60%), nausea (40-50%), arthralgias (30-35%), malaise (30-80%)
- **Rash** 30-40% (↑ HIV, peds)
 - After 5d onset
- Cytopenias, ↑ transaminases, ↓ sodium
- **CNS** disease 20% (cognitive impairment predictor)
- Pulmonary 20-25%, bldg
- 3% case fatality

HGA

- Similar symptoms
- Less rash (10%)
- CNS – lower rates
- **Morulae** 8-20%
- 1 % case fatality

Ehrlichia vs. Lyme

HGA (HGE)

- *I. scapularis/pacificus*
- Small mammal reservoir
- May-Jul
- 5-11d incubation
- M:F – 2:1
- Age 43-60
- Leukopenia – 50%
- ↓Plt – 92%
- Anemia – 50%
- ↑LFT – 91%

Lyme

- *I. scapularis/pacificus*
- Small mammal reservoir
- May-Jul
- 7-10d incubation
- 1:1
- 1.7x more freq < age 15
- Leukopenia – rare
- ↓Plt – rare
- Anemia – 12%
- ↑LFT – 19%

Questions

- Which rickettsial disease has an animal reservoir? Q fever (*Coxiella burnetii*)
- Which antibiotic is the best empiric choice if concerned re: a rickettsial disease? Doxy
- What type of bacteria causes both Spotted fever group and Typhus group of disease? Gram-negative obligate intracellular
- More likely to have multiple eschars? *R. africae* (African tick bite fever)